REMARKS

Claims 10-15 have been rejected solely under 35 USC § 103 as being unpatentable over Stoddard *et al.*, US Patent No. 5,834,231 ("Stoddard") in view of (1) Hancock *et al.*, FEMS Microbiology Letters, Vol. 186, p. 245-250 (2000) ("Hancock"); (2) Shinjoh *et al.*, Applied and Environmental Microbiology, Vol. 61, No. 2, p. 413-420 (1995) ("Shinjoh"); (3) Smirnoff *et al.*, Annu. Rev. Plant Physiol. Plant Mol. Biol., Vol. 52, p. 437-67 (2001) ("Smirnoff"); and (4) Hancock & Viola, TRENDS in Biotechnology, Vol. 20, No. 7, p.299-305 (2002) ("Hancock & Viola"). (Paper No. 20070910 at 2).

The rejection is respectfully traversed.

Stoddard discloses "a process for the production of 2-keto-L-gulonic acid by fermentative conversion of L-sorbose and/or D-sorbitol." (Stoddard, abstract). Stoddard further discloses that "the starting material, L-sorbose, may be present in the medium..., or may be generated in situ by fermentative conversion of D-sorbitol." (*Id.* at column 5, lines 26-33).

Hancock discloses the production of L-aldonolactone from L-galactose in the yeast *Saccharomyces cerevisiae.* (*See e.g.*, Hancock, abstract).

Shinjoh discloses a process for the production of 2-keto-L-gulonic acid (2-KGA) from L-sorbosone using a genetically modified strain of *G. oxydans* IFO 3293, which expresses an exogenous L-sorbosone dehydrogenase. (*See e.g.*, Shinjoh abstract).

Smirnoff is a review article which discloses the biosynthesis of vitamin C from various substrates in different organisms such as yeast, animals, and plants. (*See e.g.*, Smirnoff, Figures 1 and 3.).

Hancock & Viola is also a review article, which discloses the production of vitamin C in bacteria, plants, microalgae, and yeasts. (*See e.g.*, Hancock & Viola, Figures 2, 3 and 5). Both review articles disclose that the synthetic pathways of the various organisms are quite different (*See e.g.* Smirnoff at page 440, lines 11-13; Figure 1 and Figure 3; and Hancock & Viola, Figures 2, 3 and 5).

In making the rejection, the Examiner asserted that "Stoddard [] teaches a process for the production of L-aldonolactone (2-keto L-gluconic acid) from L-sorbose by *G. oxydans* IFO 3293...(see abstract, column 5, lines 47-48, column 6, line 10, and 60, column 14, line 10)." (Paper No. 20070910 at 3). The Examiner further asserted that "Hancock [] teaches a process wherein a growing culture of a microorganism (*S. cerevisiae*) produce L-galactono-1,4-lactone (L-aldonolactone) from a L-galactose (L-aldohexose)." (*Id.*) Additionally, the Examiner asserted that "Shinjoh [] teaches a genetically modified strain of *G. oxydans*[,] IFO 3293[,] expressing the gene encoding membrane-bound L-sorbosone dehydrogenase to improve the yield of 2-keto-L-gluconic acid (L-aldonolactone)." (*Id.* at 4.) Furthermore, according to the Examiner, "Smirnoff [] discloses a novel enzyme L-galactose dehydrogenase that oxidizes L-galactose to L-gactono-1,4-lactone [*sic*]... and [that] has been purified and cloned, L-galactose dehydrogenase recognizes L-gulose, L-sorbosone and L-fucose, with a 45%

similarity to the amino acid sequence of *Pseudomonas* L-fucose [d]ehydrogenase." (*Id.*) Moreover, the Examiner asserted,

> Hancock & Viola recites "genetic engineering has been used in strain improvement to enhance yields ... Gluconobacter *oxydans* is the species of choice for this purpose";..."recent resolution of the primary L-ascorbic acid pathway in higher plants will offer additional tools for process improvement via genetic engineering";...and..."yeast cells are known to accumulate L-ascorbic acid when grown in the presence of non-physiological substrates L-gulonolactone, L-galactonolactone or L-galactose.... [Additionally,] Hancock & Viola recites L-galactose and L-galactonolactone as a cheap source of starting substrate (p. 303, Col. 2, Lines 2-3) and further discloses "the isolation of genes involved in L-ascorbic acid biosynthesis in plants might provide useful biochemical tools to extend the metabolic capacity of industrial microorganisms (p.303, Col. 2, Lines 8-12). (Paper No. 20070910 at 4)

The Examiner then cocluded that "it would have been obvious to one of ordinary skill in the art to obtain a strain of *G. oxydans* IFO 3293 (or *P. putida*) capable of converting L-galactose or L-gulose to L-galactono-1,4 -lactone or L-gulonolactone by cloning the gene encoding the enzyme as taught by Shinjoh [] and Smirnoff [], for the purpose of improving and enhancing the yield of the production of L-aldonolactone from L-aldohexose." (*Id.* at 5). The reason, contended by the Examiner, is that "genetically engineered *G. oxydans* IFO 3293 was being used to convert intermediates of [the] L-ascorbic acid pathway, to achieve the predictable results of extending the metabolic capacity of industrial microorganisms, to increase yield, and to lower the cost of the production by providing the ability to use cheap substrates L-galactose and L-galactonolactone." (*Id.* at 5).

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In*

re Oetiker, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the documents relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to combine documents must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to combine should "***be based on objective evidence <u>of record</u>***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added).

Here, the rejection is devoid of objective evidence of record in support of the proposed combination. The Examiner asserted that the reason for the combination is that "**genetically engineered** *G. oxydans* IFO 3293 was being used to convert intermediates of [the] L-ascorbic acid pathway, to achieve the predictable results of extending the metabolic capacity of industrial microorganisms, to increase yield, and to lower the cost of the production by providing the ability to use **cheap substrates** L-galactose and L-galactonolactone." (Paper No. 20070910 at 5, emphasis added).

Initially, we note that the present application claims a process for the production of L-aldonolactone from L-aldohexose by a microorganism belonging to the genus *Pseudomonas* or *Gluconobacter* capable of producing L-aldonolactone from L-aldohexose, and, optionally, isolating the L-aldonolactone from the reaction mixture, wherein the L-aldonolactone is selected from the group consisting of L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, and L-galactonic acid and the L-aldohexose is selected from L-gulose or L-galactose. The microorganisms within the scope of the claim is not **required** to be genetically engineered to express any exogenous genes (while they could be so genetically engineered). (*See e.g.*, Examples 1 and 2, wherein the strains used were not genetically engineered to express any exogenous genes). Therefore, whether "genetically engineered *G. oxydans* IFO 3293 was being used to convert intermediates of L-ascorbic acid pathway, to achieve the predictable results of extending the metabolic capacity of industrial microorganisms, to increase yield" is irrelevant as a reason for proceeding with the present invention and cannot be a motivation factor. (Paper No. 20070910 at 5).

Furthermore, the Examiner's assertion that L-galactose and L-galactonolactone are "cheap substrates" is contrary to the evidence presented in the documents cited. (*Id.*) As set forth above, the Examiner alleged that "Hancock & Viola recites L-galactose and L-galactonolactone as a cheap source of starting substrate (p. 303, Col. 2, Lines 2-3)." To give the entire context of the Examiner's cite, page 303, column 2, lines 1-3 of Hancock & Viola discloses "[t]he **exploitation potential depends on the ability** to secure a cheap source of starting substrate ([L-galactose] or [L-galactonolactone])." Contrary to the Examiner's assertion, Hancock & Viola discloses

"[L-galactose] is an extremely rare sugar and **cheap supplies are not available**." (Hancock & Viola at page 303, column 2, lines 6-8). Therefore, the evidence of record actually goes against the Examiner's assertion: that a person skilled in the art would not be motivated to use L-galactose as a starting substrate because cheap supplies are ***not*** available.

As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here, because she has failed to provide objective evidence of record to support her assertions, and in fact, the evidence of record disproves her position. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

We further note that the rejection fails to identify the differences between the presently claimed process and the cited documents. But this is clear error. As is well settled, part of making a prime facie case, which as noted above is the Examiner's burden, is to identify on the record the differences between the claimed invention and the cited art. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966); *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). Because the Examiner failed to

identify any differences between the recited claims and the cited art, the rejection is insufficient as a matter of law and must be withdrawn.

Notwithstanding the legally deficient nature of the rejection, we note that the rejection is factually insufficient to support a rejection under § 103(a). In doing so, we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

The Examiner asserted that "Stoddard [] teaches a process for the production of L-aldonolactone (2-keto-L-gluconic acid) from L-sorbose by *G. oxydans* IFO 3293." (Paper No. 20070910 at 3). The Examiner's assertion, however, is incorrect. Stoddard discloses "[a]ny microorganism or mixture of microorganisms that can **convert D-sorbitol to L-sorbose** in the presence of NRRL B-21627 (ADM X6L) or a mutant or variant thereof while not adversely affecting its ability to convert L-sorbose to [2-keto-L-gluconic acid] may be employed [in the generation of L-sorbose fermentative conversion of D-sorbitol]." (*Id.* at column 5, lines 42-46, emphasis added). One of such microorganisms **for the conversion of D-sorbitol to L-sorbose** is "*Gluconobacter oxydans*, more preferably *G. oxydans* strain ATCC 621 or *G. oxydans* strain IFO 3293." (*Id.* at column 5, lines 47-49). Indeed, in example 6 of Stoddard

(which was cited by the Examiner), *G. oxydans* mutants were used as "a second microorganism having the capability of converting D-sorbitol to L-sorbose." (*Id.*, column 13, line 66 and column 14, lines 1-2). Thus, Stoddard's disclosure with respect to *G. oxydans* IFO 3293 only applies to the conversion of **D-sorbitol to L-sorbose**, not from the conversion of **L-sorbose to L-aldonolactone**. Accordingly, the Examiner's assertions with respect to Stoddard are factually inaccurate.

Furthermore, assuming *arguendo* that all five documents cited by the Examiner are properly combinable, which they are not, such a combination does not produce the process of claims 10-15.

Shinjoh and Soddard both disclose the use of **different substrates**, *e.g.* L-sorbose or D-sorbitol (vs. L-galactose or L-glactonolactone recited in the presently claimed process). Therefore, there is a factual gap that these documents do not fill, namely, that the D-sorbitol/L-sorbose pathway in *G. oxydans* can be used for substrates as different as L-galactose and L-gulose. Specifically, L-sorbose contains a keto-group, whereas L-galactose and L-gulose contain an OH-group, *i.e.* are in a different oxidation state. A different oxidation state means, *inter alia,* different distribution of electrons and/or different optical or chemical activity, and thus different enzymatic reactions within a microorganisms in order to convert such different substrates. The conversion of L-sorbose occurs through enzymes such as L-sorbosone dehydrogenase (SNDH) or L-sorbose dehydrogenase (SOH) as disclosed, *e.g.*, in Shinjoh (see *e.g.* page 414, Fig. 1), or in Figure 2 of Hancock & Viola. These enzymes have only a limited and highly specific substrate activity. One skilled in the art would not expect them to react with L-galactose and L-gulose.

Because, as noted above, the rejection did not carry out a proper Graham analysis, it failed to recognize that none of the other documents cited by the Examiner can fill this gap. Hancock discloses the production of L-galactono-1,4-lactone in **a different organism**, the yeast *Saccharomyces cerevisiae* (vs. bacteria including *G. oxydans*). The conversion of L-galactose in yeast occurs through the "pathway naturally used for [D-erythroascorbic acid]". (Hancock, abstract). As one skilled in this art knows, the yeast pathway is entirely different from the D-sorbitol/L-sorbose pathway in *G. oxydans*. (Compare Figure 1 of Hancock to Figure 1 of Shinjoh.) Moreover, there is no disclosure in Hancock (or in Shinjoh or in Stoddard) that the finding in the yeast is applicable to other microorganisms, such as *Gluconobacter* or *Pseudomonas*.

Smirnoff is silent as to: (i) whether the D-sorbitol/L-sorbose pathway is able to convert L-galactose or L-gulose and (ii) whether the yeast pathway is applicable to *Gluconobacter* or *Pseudomonas*. In fact, Smirnoff discloses that the synthetic pathways of plants, bacteria, microalgae and yeasts are vastly different. (*See e.g.*, Smirnoff at page 440, lines 11-13; and Figures 1 and 3.) The Examiner cited Smirnoff for disclosing that L-galactose dehydrogenase purified and cloned from **plants** is involved in the generation of L-galactono-1,4-lactone from L-galactose. (Smirnoff at 444-445). The fact that such an enzyme is found in plants does not mean that they are found in other organisms. The Examiner also appeared to suggest that once the plant gene for such an enzyme is found, bacteria can be genetically engineered to express this plant gene. (*See* Paper 20070910 at 5, lines 1-4). As discussed above, however, the process claimed by the present application does not require bacterial strains to express such an exogenous plant gene. Additionally, the Examiner asserted that

Smirnoff disclosed that this enzyme has about "45% **similarity** [not identity] to the amino acid sequence of *Pseudomonas* L-fucose dehydrogenase." (Smirnoff at 445, lines 14-15, emphasis added.) As is well known to one skilled in this art, 45% sequence similarity is not an indication of similarity in function.

The addition of the Hancock & Viola does not close the gaps either. The Examiner cited to Hancock & Viola as disclosing: (i) genetic engineering of microorganisms, (ii) L-galactose as a source of cheap substrates, and (ii) yeast cells' ability to accumulate L-ascorbic acid when grown in the presence of non-physiological substrates such as L-galactose. (Paper No. 20070910 at 4). As set forth above, the claimed process encompasses organisms that do not express exogenous genes. Furthermore, the assertion that Hancock & Viola discloses L-galactose and L-galactose are sources of cheap substrates is incorrect. Lastly, the synthetic pathways of yeast and other microorganisms (or other organisms for that matter) are vastly different, as disclosed by Smirnoff and again by Hancock & Viola. In fact, Hancock & Viola provides an excellent illustration of the vast differences in the structures of the substrates, the intermediates and the final products, as well as the enzymes involved in the pathways converting L-sorbose and L-galactose in the different organism (compare the right half of Figure 2 of Hancock & Viola to Figure 5 of the same document).

At bottom, the Examiner has yet to come to grips with these glaring factual differences. It is respectfully submitted that Stoddard, Shinjoh, Hancock, Smirnoff, and Hancock & Viola do not alone or in combination disclose or suggest claims 10-15. In view of the foregoing, it is respectfully submitted that the rejection is

deficient as a matter of fact and law. Therefore, withdrawal of the rejection is respectfully requested.

Accordingly, for the reasons set forth above, entry of the amendments and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box. 1450 Alexandria, VA 22313-1450, on April 8, 2008.

Jihong Zang, Reg. No. 56,606

Respectfully submitted,

By: _____

Jihong Zang
Reg. No. 56,606
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
Phone: (212) 541-2000
Fax: (212) 541-4630